ORIGINAL ARTICLE

Blood Poisoning of Cancer Patients Resulting from the Use of Paisali Containing Mixed Cannabis

Sakchai Sriklang

Department of Public Health, Faculty of Science, Buriram Rajabhat University, Mueang Buriram 31000, Buriram, Thailand

ABSTRACT

Introduction: The prevalence of cancer patients seeking the Paisali formula from researchers in collaboration with Khu Muang Hospital during the year 2022 reflects the cancer patients' inclination towards exploring herbal remedies for cancer treatment. **Methods:** This study aimed to investigate the effectiveness of the Paisali formula in alleviating vomiting and hematological toxicity in cancer patients using an experimental approach. The study comprised a total of 400 participants divided into two groups: an experimental group of 200 individuals receiving the Paisali drug and a control group of 200 individuals receiving a placebo. Throughout the study, toxicity levels were evaluated through laboratory blood tests conducted five times at 30-day intervals, and the results underwent independent t-test analysis. **Results:** The experimental group, which received 200 mg of Paisali, exhibited a statistically significant reduction in post-chemotherapy vomiting ($p<0.00$). Additionally, a comparison of blood test results before and after the administration of Paisali between the experimental and control groups revealed noteworthy differences in hydrogen ion concentration, hemoglobin levels, hematocrit, neutrophil count, alkaline phosphatase, aspartate transaminase, total bilirubin, and blood sugar values ($p<0.00$), as well as white blood cell values ($p<0.02$). These results suggest that the Paisali formula not only effectively reduced vomiting but also ameliorated hematological toxicity when compared to standard treatment alone. **Conclusion:** This study offers valuable insights into the potential advantages of incorporating the Paisali formula as an additional treatment option for managing chemotherapy-induced side effects in cancer patients. However, further research is necessary to comprehensively explore its mechanisms and long-term effects.
Malaysian Journal of Medicine and Health Sciences (2024) 20(3): 112-118. doi:10.47836/mjmhs.20.3.16

Keywords: Herbals, Blood Poisoning, Cannabis, Cancer, Vomiting

Corresponding Author:
Sakchai Sriklang
Email: sukchai.sr@bru.ac.th
Tel: +66822019129

INTRODUCTION

Metabolic acidosis is a prevalent form of acid-base imbalance disorder. In patients with poisoning or overdose (1-4), it arises from an elevation in hydrogen ions and chloride ions (Cl) or a depletion of bicarbonate ions, accompanied by an increase in chloride ions to maintain equilibrium. Meanwhile, the wide anion gap is due to the buildup of certain unmeasured anions in the blood, such as lactic acid (5-8). When combined with cannabis, this condition is mainly caused by the quantity consumed per session (unit dose) and the user's tolerance. Introduction of cannabis into the body can lead to overdose, hence it should not be considered as the primary treatment option (9-12). Instead, it is advisable to start with small doses and gradually increase them.

THC and CBD refer to substances classified under the cannabinoid group, each exhibiting different effects. For instance, Tetrahydrocannabinol (THC) has pain-relieving and muscle-relaxant properties. Currently, it is used to alleviate nausea after chemotherapy and to stimulate appetite in patients with AIDS or Anorexia. On the other hand, Cannabidiol (CBD) induces a calming sensation and counteracts the effects caused by THC. THC and CBD-induced metabolic acidosis result from drug interactions. Co-administration with other drugs alters blood levels of THC and CBD because THC is metabolized by cytochrome P450 (CYP), specifically CYP2C9, CYP2C19, and CYP3A4 (13-17). CBD, on the other hand, is metabolized by CYP2C19 and CYP3A4 (13). When THC and CBD are taken together with enzyme inducers, their blood levels decrease (18, 19). Conversely, when THC and CBD are used alongside drugs that inhibit CYP450, especially CYP2C19 and CYP3A4, the levels of THC and CBD in the blood can increase to toxic levels (20, 21). Furthermore, pyroglutamic acidosis can be caused by drugs that interfere with the γ-glutamyl cycle, which is responsible for generating the antioxidant glutathione. This disruption leads to wide anion gap metabolic acidosis, as seen in the effect on glutathione in the analgesic group, including THC and

CBD. Glutathione reduction leads to the conversion of γ-glutamyl cysteine to pyroglutamic acid (5-oxoproline) (22-24). Such acidosis may occur in patients with a history of alcohol use or impaired liver or kidney function (25).

Paisali texts are categorised as medicinal formulas in Ayur-Veda Studies 6, Volume 2 by Khun Nitthesukkij. These texts have been accompanied by recipes of Thai royal medicines since the Ayutthaya period, and some of these recipes mention the properties of cannabis or contain cannabis. Specifically, there are 3 formulas from Phra Narai's medicine scriptures, 2 formulas from the reign of King Rama II, and 14 formulas from Wat Pho inscriptions, totaling 22 formulas, along with 90 cannabis-containing medicinal formulas from Thai traditional medicine (out of about 2,300 published national formulas) (26). Originally, Paisali formula was traditionally employed to address conditions such as abdominal discomfort, indigestion, mucus expulsion, nausea reduction, and dizziness. The diagnosis of septicemia is categorised into pathologic, physiological, and therapeutic types. This diagnosis is made by synthesising the clinical history, conducting physical examinations, and analysing serum and urine chemistry, arterial blood gases, electrolytes, osmolality gap calculation (27-31), kidney function tests, liver function tests, and blood sugar testing (32). Khu Mueang Hospital has been using cannabis analgesics in cancer patients for five years, with a THC to CBD ratio of 1:1 or a dose of 27 mg THC and 25 mg CBD per tablet. These cannabis analgesics are indicated for cancer patients experiencing pain and loss of appetite. Another formulation containing 25 mg of CBD (33, 34) is indicated for patients with epilepsy and Parkinson's disease. Good treatment results were observed when maintaining CBD levels between 10-40 mcg/ml (35, 36). Blood samples were taken before and after drug administration, and monthly follow-ups were conducted to assess treatment effectiveness.

Hence, toxicity monitoring for drug use is primarily carried out to evaluate clinical treatment. It is essential to expedite correction and research to establish a comprehensive understanding of treatment, leading to the development of a drug policy and determining the appropriate drug dosages for patients, including the safe herbal formula Paisali. Consequently, the researcher aims to investigate blood poisoning as a knowledge foundation for the future secure and effective usage of medicinal herbs. The research's objective was to compare the prevalence of blood poisoning before and after administering a medicinal cannabis-containing Paisali formula to cancer patients treated at a Thai traditional medicine clinic, Khu Mueang Hospital. Additionally, the study sought to establish the correlation between dosage and effectiveness in managing chemotherapy-induced vomiting in cancer patients. The ultimate goal is to create guidelines for the future use of the Paisali formula.

MATERIALS AND METHODS

This study represents experimental research (Experimental study) that took place from January to December 2022, and was scrutinized by the Human Research Ethics Committee at Buriram Rajabhat University. The evaluation of results (Double-blind randomized controlled trial) (37) involved 200 participants who were randomly assigned. The aim was to investigate the correlation between dosage and the alleviation of vomiting in cancer patients after chemotherapy, as well as to juxtapose the pre- and post-treatment blood test results, using the Paisali medicinal formula.

Population

Cancer patients undergoing treatment at the Thai Traditional Medicine Clinic, Khu Mueang Hospital, from 1st January 2021 to 31st December 2022.

Sample Group

The study utilised a sample group comprising 200 individuals selected from the database of the Thai traditional medicine clinic at Khu Mueang Hospital. The sample size was determined using the formula for calculating sample size in experimental research (38) with two groups of samples (experimental group and control group), accounting for an anticipated attrition rate of 10% (R=0.1). The inclusion criteria for research participants were as follows: (1) patients diagnosed with cancer ranging from stage 1 to stage 4; (2) cancer patients undergoing chemotherapy; and (3) cancer patients who provided their informed consent to participate in the study.

Selection Criteria

The eligibility criteria involve patients with well-established awareness and cognitive functioning, capable of understanding and willingly participating in the research. These individuals are actively seeking services that involve the administration of the Paisali formula. Medical indications for cannabis use encompass patients undergoing chemotherapy, those dealing with pain, nausea, and vomiting, as well as individuals facing challenges related to sleep disturbances.

Exclusion criteria include pregnant patients, breastfeeding mothers, a history of allergies to cannabis extracts or coconut oil, patients with heart or liver diseases, severe kidney impairment, those taking blood clotting medications, individuals with psychiatric conditions (schizophrenia, bipolar disorder, depressive disorder), or those with suicidal ideation or attempts.

Sampling

In this study, systematic random sampling was employed (39). The patients were arranged in alphabetical order, and a total of 200 patients were included for data analysis.

Ethical Approval
This research employs an experimental research design using two sample groups: a control group and an experimental (case) group. Measurements are taken before and after the intervention, and standardization ensures that both sample groups are in the same environment. The safety of the volunteers is a priority, and the researchers have outlined the objectives, providing a research participation consent form. This study has obtained ethical approval from the Research Ethics Committee for Human Research at Buriram Rajabhat University, certified under number 012/2022.

Data Collection
In this study, the data was gathered by the researcher through blood collection and laboratory testing, acquiring the subsequent data: personal characteristics, blood test values prior to and subsequent to Paisali consumption, with analysis of metabolic acidosis levels, complete blood count (CBC), blood urea nitrogen (BUN), serum creatinine (CR), urine output, liver function test, and blood sugar test, among others.

Composition of the Paisali Formulation
The components of the Paisali formulation include 3.75 grams of *Diospyros decandra*, 3.75 grams of *Myristica fragrans*, 5.625 grams of *Amomum testaceum*, 7.5 grams of *Syzygium aromaticum*, 9.375 grams of *Piper longum*, 11.25 grams of *Ardisia polycephala*, 13.125 grams of *Acorus calamus*, 15 grams of rock salt, 1.875 grams of *Nigella sativa*, 24.375 grams of *Trachyspermum ammi*, 26.25 grams of *Cinnamomum camphora*, 28.125 grams of *Terminalia arjuna*, 22.5 grams of *Foeniculum vulgare*, 30 grams of *Terminalia chebula*, 31.87 grams of *Terminalia bellirica*, 35.62 grams of *Atractylodes lancea*, 26.25 grams of *Amorphophallus saraburiensis*, 29.37 grams of dried ginger, 26.25 grams of *Plumbago indica*, 75 grams of *Micromelum minutum*, 450 grams of cannabis, and 900 grams of long pepper.

The procedural steps involve the screening of eligible patients and obtaining treatment information before entering the treatment phase. Prior to usage, patients are advised to drink a mixture of water, honey, and lime with a pinch of salt in the first week. Starting from the first week, patients are instructed to consume the Paisali medication at a daily dosage of 200 milliliters. If the symptoms improve, the dosage is gradually reduced every week. Patient follow-up is conducted for the initial 4 weeks, after which appointments are scheduled monthly for a duration of 3 months. Patient conditions are assessed before and after treatment through laboratory poisoning blood tests.

Research Instruments
This study employed a diagnostic test (40) to assess or identify toxicity in cancer patients undergoing treatment at Khu Mueang Hospital, a Thai traditional medicine clinic. The aim was to utilize the test outcomes to rectify deficiencies and enhance the effectiveness of cannabis herbal remedies for treatment advancement.

Statistical analysis
This study employs a descriptive research model to present frequency and percentage distributions for describing categorical data, encompassing personal characteristics and general information. The analysis incorporates Chi-square and Independent t-test techniques (41). The objective is to assess the hypothesis regarding the correlation between dosage and the alleviation of vomiting among cancer patients post-chemotherapy. Additionally, it involves a comparison of results from pre- and post-treatment blood examinations subsequent to the administration of the Paisali formula. These assessments include parameters such as metabolic acidosis, complete blood count (CBC), blood urea nitrogen (BUN), serum creatinine (CR), urine output, liver function test, and blood sugar test.

RESULTS

General Information of the Population
An overview of the general information from the experimental group reveals that recipients of the Paisali formula included both males and females. Those over the age of 55 constituted 50% of the group, followed by the age bracket of 46 to 55 years, which made up 65.50% of the participants. Additionally, 89.50% of the individuals were non-smokers. The average systolic blood pressure stood at 140.40 with a standard deviation of 3.20. The range for systolic blood pressure was from a minimum of 110 to a maximum of 130. The average diastolic blood pressure was recorded at 74.37 with a standard deviation of 7.04. Diastolic blood pressure ranged from a minimum of 60 to a maximum of 96. Oxygen saturation exhibited an average value of 90.56 with a standard deviation of 5.03. The range for oxygen saturation was from a minimum of 82 to a maximum of 99 (Table I).

Comparison of Laboratory Results Between Individuals Administered Paisali (Experimental Group) and Those Not Administered Paisali (Control Group)
The results of the analysis of laboratory blood tests, which compare the effectiveness of treatment and bloodstream toxicity in patients receiving Paisali (experimental) versus those not receiving Paisali (control), were obtained by examining biochemical parameters. These parameters encompassed assessments for metabolic acidosis, complete blood count, kidney function tests, liver function tests, and blood sugar tests. Significant differences in hydrogen ion values were observed between the experimental group receiving Paisali and the control group not receiving Paisali (p-value = 0.000). Similarly, Significant differences were noted in hemoglobin values (p-value = 0.000), hematocrit values (p-value = 0.000), neutrophil values (p-value = 0.000), alkaline phosphatase values (p-value = 0.000), aspartate

Table I: Numbers, percentages, mean, standard deviation, maximum, and minimum values for individuals receiving the Paisali formula

General Information	Case (200)	
	Numbers	Percent (%)
Gender		
- males	100	50
- females	100	50
Age		
- under 25 years	0	0
- 25 - 35 years	6	3.00
- 36 - 45 years	19	9.50
- 46 - 55 years	44	22.00
- over 55 years	131	65.50
Mean; S.D. (61.13; 13.99)		
Max; Min (87; 25)		
Smoking history		
- non-smokers	179	89.50
- smokers	21	10.50
Blood pressure (mmHg)		
- Systolic *blood pressure* Mean; S.D. (120.4; 3.20) Max; Min (130; 110)		
- Diastolic *blood pressure* Mean; S.D. (74.37; 7.04) Max; Min (96; 60)		
Oxygen saturation		
Mean; S.D. (90.56; 5.03) Max; Min (99; 82)		
Pulse rate (beats/mins)		
Mean; S.D. (76.15; 3.36) Max; Min (81; 70)		
Respiratory rate (times/mins)		
Mean; S.D. (22.27; 2.35) Max; Min (26; 19)		
Body Temperature (Degrees Celsius)		
Mean; S.D. (36.81; 0.49) Max; Min (37.6; 35.5)		

Keys: mmHg = millimeters of mercury; min = minutes

transaminase values (p-value = 0.000), total bilirubin levels (p-value = 0.000), and blood sugar values (p-value = 0.000) between those who were administered the Paisali formula in the experimental group and those who were not administered it in the control group (Table II). White blood cell values also displayed significant differences between the two groups, with a p-value of 0.027.

The Correlation Between Drug Dosage and Alleviation of Vomiting in Cancer Patients Post Chemotherapy

The results from the analysis of the correlation between drug dosage and the alleviation of vomiting in cancer patients post chemotherapy indicated that the employment of a dosage factor of 200 mg per body weight was linked to a statistically significant decrease in vomiting symptoms among cancer patients post chemotherapy (p-value = 0.0001) (Table III).

DISCUSSION

This research aimed to investigate the effectiveness of alleviating vomiting in cancer patients following chemotherapy and septicemia in cancer patients through an experimental study. The researcher maintained the confidentiality of the personal details of the research participants. Those in the experimental group, after a three-month regimen of Paisali, observed a noteworthy decrease in vomiting among cancer patients following chemotherapy. This therapeutic effect exhibited statistical significance ($p<0.05$). This result aligns with the research by Grimison et al. (42-45), who explored the use of cannabis in alleviating boredom, nausea and vomiting resulting from chemotherapy through sublingual administration, with doses ranging from 2.05 to 2.58 ng/mL (46-48). The Paisali formula may potentially induce Lactic acidosis, a condition arising from the use of medication that impacts the functioning of the liver—an organ crucial for drug metabolism. This condition can have consequences on the patient's quality of life akin to the results of McHugh et al. (49) and Marconi et al. (50), who investigated the effects of cannabis usage at dosages of 1.93, 12.44, 490, and 2000 g/bw respectively, and identified its impact on mental health changes.

Additionally, this research revealed significant statistical differences ($p<0.05$) in the laboratory test results of the experimental group compared to the control group. Parameters such as hydrogen ion, hemoglobin, hematocrit, white blood cell count, neutrophil count, alkaline phosphatase, aspartate transaminase, total bilirubin, and blood sugar demonstrated notable variations. An abnormally low Hemoglobin level can negatively impact cells, causing either cell swelling or cell death. Furthermore, assessing liver function through markers like Aspartate Transaminase and bilirubin with decreased values may pose a potential risk to the proper functioning of the liver. However, blood test results for parameters including bicarbonate, platelet count, blood urea nitrogen, creatinine, total protein, and albumin did not exhibit statistically significant differences ($p<0.05$). This could potentially be attributed to the natural physiological adaptation of the body, as it strives to maintain balance.

The Paisali formulation causes disruptions in enzymes crucial for the body's metabolic processes, leading to an inadequate oxygen supply to cells (Anaerobic condition). This results in the production of lactic acid through the transfer of electrons from NADH to pyruvate, facilitated by the enzyme Lactate Dehydrogenase (LDH). This toxicity poses risks to the liver, responsible for drug metabolism, and may affect overall bodily functions.

Following the use of the Paisali medication formula, its antiemetic properties are realized through the inhibition of dopamine receptors in the Chemoreceptor Trigger Zone, suppressing the vomiting reflex. Additionally, the medication can inhibit dopamine receptors along the gastrointestinal tract.

Table II: Comparison of blood test results prior to and following administration of Paisali formula

Biochemical Parameter	Mean		MD	t	df	95%CI of MD	*P*-value
	pre-treatment	post-treatment					
1. Metabolic acidosis							
1.1 Hydrogen ion	7.35	7.47	-0.12	-4.43	199	-0.18 to -0.07	<0.0001
1.2 Bicarbonate	24.05	23.97	0.07	0.68	199	-0.13 to 0 .28	<0.245
2. Complete blood count							
2.1 Hemoglobin	13.79	13.68	0.11	3.43	199	0.04 to 0.18	<0.0004
2.2 Hematocrit	40.38	41.22	-0.84	-4.13	199	-1.24 to -0.43	<0.0001
2.3 White Blood Cell	7305.16	7471.50	-166.34	-1.92	199	-336.70 to 4.02	<0.027
2.4 Neutrophil	52.13	56.45	-4.32	-10.35	199	-5.14 to -3.50	<0.0001
2.5 Platelet	8399772	7798065	601707	0.20	199	-5203621 to 6407036	<0.419
3. Kidney function test							
3.1 Blood Urea Nitrogen	17.30	16.58	0.71	0.83	199	-0.98 to 2.41	<0.202
3.2 Creatinine	0.74	0.73	0.00	0.14	199	-0.05 to 0.06	<0.441
4. Liver function test							
4.1 Alkaline phosphatase	96.56	106.87	-10.31	-6.39	199	-13.49 to -7.13	<0.0001
4.2 Aspartate transaminase	29.66	28.99	0.66	3.86	199	0.32 to 1.00	<0.0001
4.3 Total bilirubin	0.67	0.59	0.07	4.60	199	0.04 to 0.10	<0.0001
4.4 Total protein	7.54	7.67	-0.13	-0.52	199	-0.62 to 0.35	<0.298
4.5 albumin	4.32	6.57	-2.25	-1.06	199	-6.43 to 1.93	<0.145
5. Blood sugar test							
5.1 blood sugar	86.88	107.46	-20.57	-18.48	199	-22.77 to-18.38	<0.0001

Keys: MD = mean difference; t = a ratio of the difference between the mean of the two sample sets and the variation that exists within the sample sets.; df = degrees of freedom; CI = confidence interval; P = probability

Table III: Effectiveness of Paisali formula in alleviating vomiting in cancer patients after chemotherapy

Drug Dosage	Chemotherapy induced nausea and vomiting		
	Mixed Effect	95% CI	*p*-value
200 mg/bw	2.66	0.26-0.04	0.0001
400 mg/bw	1.60	0.12-0.10	0.10
1,200 mg/bw	0.07	0.15-0.14	0.94

Keys: mg/bw = milligrams per body weight; CI = confidence interval; P = probability

From the results of this research, it affirms the indication of the Paisali formula, grounded in the traditional medical wisdom of Thailand, which employs the Paisali formula to alleviate feelings of nausea and vomiting through a holistic medical approach. This approach elucidates the interconnection between the body and pathogenesis, employing elemental theory that aligns with contemporary medical guidelines. The process commences with a comprehensive patient history and culminates in an accurate diagnosis of the condition. Nonetheless, this study's focal point remains the application of the Paisali formula in relation to the aforementioned illnesses and symptoms. The results of the research may not be fully expounded upon by the tenets of Thai traditional medicine and modern medical principles. Consequently, further investigation into the blood poisoning in cancer patients or other detrimental occurrences is warranted. Such research will underscore the effectiveness and confidence in employing the Paisali treatment in cancer cases.

CONCLUSION

This study revealed that the consumption of the Paisali formula at a daily dosage of 200 milligrams over a 3-month period effectively alleviated post-chemotherapy nausea in cancer patients. Laboratory blood tests conducted before and after the medication did not exhibit significant variations, suggesting the absence of blood toxicity risks associated with the Paisali formula. The observed decline in liver function tests may be attributed to molecular aspects of the medication and individual patient characteristics. This emphasizes the essential role of pharmacokinetics in drug usage to maintain effectiveness for patients in the long term.

ACKNOWLEDGEMENTS

The author wishes to express gratitude to all researchers hailing from the Department of Public Health Sciences, Faculty of Science, Buriram Rajabhat University, for their invaluable support in facilitating this research.

REFERENCES

1. Abeysekara S, Zello GA, Lohmann KL, Alcorn J, Hamilton DL, Naylor JM. Infusion of sodium bicarbonate in experimentally induced metabolic acidosis does not provoke cerebrospinal fluid (CSF) acidosis in calves. Can J Vet Res. 2012;76(1):16-22.

2. Achanti A, Szerlip HM. Acid-Base Disorders in the Critically Ill Patient. Clin J Am Soc Nephrol. 2023;18(1):102-112. doi: 10.2215/CJN.04500422.
3. Abad K, Kien C, Ganta K. A unique case of metformin-associated severe lactic acidosis without preexisting renal disease: perspectives on prolonged dialysis and education for prevention. Cureus. 2020;12(4). doi: 10.7759/cureus.7564.
4. Goonoo MS, Morris R, Raithatha A, Creagh F. Metformin-associated lactic acidosis: reinforcing learning points. BMJ Case Rep CP. 2020;13(9):e235608. doi: 10.1136/bcr-2020-235608.
5. Judge BS. Differentiating the causes of metabolic acidosis in the poisoned patient. Clinics in Laboratory Medicine. 2006;26(1):31-48. doi: 10.1016/j.cll.2006.01.002.
6. Dhatariya KK, Glaser NS, Codner E, Umpierrez GE. Diabetic ketoacidosis. Nat Rev Dis Primers. 2020;6(1):40. doi: 10.1038/s41572-020-0165-1.
7. Berend K, Duits AJ. The role of the clinical laboratory in diagnosing acid-base disorders. Crit Rev Clin Lab Sci. 2019;56(3):147-169. doi: 10.1080/10408363.2019.1568965.
8. Rudkin SE, Grogan TR, Treger RM. The Δ anion gap/Δ bicarbonate ratio in early lactic acidosis: time for another delta? Kidney360. 2021;2(1):20. doi: 10.34067/KID.0000842019.
9. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet. 2003;42(4):327-60. doi: 10.2165/00003088-200342040-00003.
10. Ang SP, Sidharthan S, Lai W, Hussain N, Patel KV, Gulati A, et al. Cannabinoids as a potential alternative to opioids in the management of various pain subtypes: Benefits, limitations, and risks. Pain Ther. 2023;12(2):355-375. doi: 10.1007/s40122-022-00465-y.
11. Edinoff AN, Wu NW, Nix CA, Bonin B, Mouhaffel R, Vining S, et al. Historical pathways for opioid addiction, withdrawal with traditional and alternative treatment options with ketamine, cannabinoids, and noribogaine: a narrative review. Health Psychol Res. 2022;10(4). doi: 10.52965/001c.38672.
12. Kansagara D, Becker WC, Ayers C, Tetrault JM. Priming primary care providers to engage in evidence-based discussions about cannabis with patients. Addict Sci Clin Pract. 2019;14:42. doi: 10.1186/s13722-019-0171-3.
13. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. British Journal of Clinical Pharmacology. 2018;84(11): 2477-2482. doi: 10.1111/bcp.13710.
14. Gussow L. Toxicology Rounds: Should EPs Worry about CBD Toxicity? Emerg Med News. 2020 Mar;42(3):17. doi: 10.1097/01.EEM.0000657672.65371.f2.
15. Smith RT, Gruber SA. Contemplating cannabis? The complex relationship between cannabinoids and hepatic metabolism resulting in the potential for drug-drug interactions. Front Psychiatry. 2023;13:1055481. doi: 10.3389/fpsyt.2022.1055481.
16. Khan H, Singh A, Thapa K, Garg N, Grewal AK, Singh TG. Therapeutic modulation of the phosphatidylinositol 3-kinases (PI3K) pathway in cerebral ischemic injury. Brain Res. 2021;1761:147399. doi: 10.1016/j.brainres.2021.147399.
17. Sadowska O, Baranowska-Kuczko M, Gromotowicz-Pop□awska A, Biernacki M, Kicman A, Malinowska B, et al. Cannabidiol ameliorates monocrotaline-induced pulmonary hypertension in rats. Int J Mol Sci. 2020;21(19):7077. doi: 10.3390/ijms21197077.
18. Bara A, Ferland JN, Rompala G, Szutorisz H, Hurd YL. Cannabis and synaptic reprogramming of the developing brain. Nat Rev Neurosci. 2021;22(7):423-438. doi: 10.1038/s41583-021-00465-5.
19. White CM. A review of human studies assessing cannabidiol's (CBD) therapeutic actions and potential. J Clin Pharmacol. 2019;59(7):923-934. doi: 10.1002/jcph.1387.
20. Alsherbiny MA, Li CG. Medicinal Cannabis-Potential Drug Interactions. Medicines (Basel). 2018;6(1):3. doi: 10.3390/medicines6010003.
21. Brown JD. Potential adverse drug events with tetrahydrocannabinol (THC) due to drug-drug interactions. J Clin Med. 2020;9(4):919. doi: 10.3390/jcm9040919.
22. Pham AQT, Xu LHR, Moe OW. Drug-Induced Metabolic Acidosis. F1000Research. 2015;4:1460. doi: 10.12688/f1000research.7006.1.
23. Saudubray JM, Garcна-Cazorla Б. Clinical approach to inborn errors of metabolism in pediatrics. In: Blau N, Duran M, Gibson KM, editors. Inborn Metabolic Diseases: Diagnosis and Treatment. Berlin, Heidelberg: Springer Berlin Heidelberg. 2022;3-123. doi: 10.1007/978-3-662-63123-2_1.
24. Buinitskaya Y, Gurinovich R, Wlodaver CG, Kastsiuchenka S. Centrality of G6PD in COVID-19: the biochemical rationale and clinical implications. Front Med. 2020;7:584112. doi: 10.3389/fmed.2020.584112.
25. Long B, Lentz S, Gottlieb M. Alcoholic ketoacidosis: Etiologies, evaluation, and management. J Emerg Med. 2021;61(6):658-665. doi: 10.1016/j.jemermed.2021.09.007.
26. Iam-am A, Thippayacharoentam T, Thippayacharoentam C, Chaiworaslip W, Duangdee T. Analytical Study of Herbal Medicine in Phrom P'Rohit Scripture. Damrong Journal of The Faculty of Archaeology Silpakorn University. 2018;17(2).

27. Fabre V, Carroll KC, Cosgrove SE. Blood Culture Utilization in the Hospital Setting: a Call for Diagnostic Stewardship. J Clin Microbiol. 2022;60(3):e0100521. doi: 10.1128/JCM.01005-21.
28. Marshall WJ, Lapsley M, Day A, Shipman K. Clinical Chemistry. 9th ed. Elsevier Health Sciences; 2020.
29. Zhang Y, Liang F, Zhang D, Qi S, Liu Y. Metabolites as extracellular vesicle cargo in health, cancer, pleural effusion, and cardiovascular diseases: An emerging field of study for diagnostic and therapeutic purposes. Biomed Pharmacother. 2023;157:114046. doi: 10.1016/j.biopha.2022.114046.
30. Penman ID, Ralston SH, Strachan MW, Hobson R. Davidson's Principles and Practice of Medicine E-Book. 24th ed. Elsevier Health Sciences; 2022.
31. Jangjou A, Moqadas M, Mohsenian L, Kamyab H, Chelliapan S, Alshehery S, et al. Awareness raising and dealing with methanol poisoning based on effective strategies. Environ Res. 2023;228:115886. doi: 10.1016/j.envres.2023.115886.
32. Fujii T, Udy AA, Nichol A, Bellomo R, Deane AM, El-Khawas K, et al. Incidence and management of metabolic acidosis with sodium bicarbonate in the ICU: An international observational study. Critical Care (London, England). 2021;25(1):45. doi: 10.1186/s13054-020-03431-2.
33. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010;39(2):167-79. doi: 10.1016/j.jpainsymman.2009.06.008.
34. Maayah ZH, Takahara S, Ferdaoussi M, Dyck JR. The anti-inflammatory and analgesic effects of formulated full-spectrum cannabis extract in the treatment of neuropathic pain associated with multiple sclerosis. Inflamm Res. 2020;69:549-558. doi: 10.1007/s00011-020-01341-1.
35. Kang JS, Lee MH. Overview of Therapeutic Drug Monitoring. The Korean Journal of Internal Medicine. 2009;24(1): 1-10. doi: 10.3904/kjim.2009.24.1.1.
36. Ghali M, Bensted K, Williams DB, Ghaly S. Type 2 autoimmune pancreatitis associated with severe ulcerative colitis: Three case reports. World J Clin Cases. 2022;10(24):8788. doi: 10.12998/wjcc.v10.i24.8788.
37. Cole EJ, Phillips AL, Bentzley BS, Stimpson KH, Nejad R, Barmak F, et al. Stanford neuromodulation therapy (SNT): A double-blind randomized controlled trial. Am J Psychiatry. 2022;179(2):132-141. doi: 10.1176/appi.ajp.2021.20101429.
38. Sharma SK, Mudgal SK, Thakur K, Gaur R. How to calculate sample size for observational and experimental nursing research studies? Natl J Physiol Pharm Pharmacol. 2020;10(01):1-8.
39. Bhardwaj P. Types of sampling in research. J Pract Cardiovasc Sci. 2019;5(3):157. doi: 10.4103/jpcs.jpcs_62_19.
40. Heuer C, Stevenson MA. Diagnostic test validation studies when there is a perfect reference standard. Revue Scientifique et Technique (International Office of Epizootics). 2021;40(1):261-270. doi: 10.20506/rst.40.1.3223.
41. Lee SW. Methods for testing statistical differences between groups in medical research: statistical standard and guideline of Life Cycle Committee. Life Cycle. 2022;2. doi: 10.54724/lc.2022.e1.
42. Grimison P, Mersiades A, Kirby A, Lintzeris N, Morton R, Haber P, et al. Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: a randomised, placebo-controlled, phase II crossover trial. Ann Oncol. 2020;31(11):1553-1560. doi: 10.1016/j.annonc.2020.07.020.
43. Bolshakova M, Bluthenthal R, Sussman S. Opioid use and misuse: health impact, prevalence, correlates and interventions. Psychol Health. 2019;34(9):1105-1139. doi: 10.1080/08870446.2019.1622013.
44. Mills L, Lintzeris N, O'Malley M, Arnold JC, McGregor IS. Prevalence and correlates of cannabis use disorder among Australians using cannabis products to treat a medical condition. Drug Alcohol Rev. 2022;41(5):1095-1108. doi: 10.1111/dar.13444.
45. Krasner S. Gender Differences in Cannabis Vaporizer Use [dissertation]. Palo Alto University; 2020.
46. Blake A, Wan BA, Malek L, DeAngelis C, Diaz P, Lao N, et al. A selective review of medical cannabis in cancer pain management. Ann Palliat Med. 2017;6(Suppl 2):S215-S222. doi: 10.21037/apm.2017.08.05.
47. Ross M. Kratom is Medicine: Natural Relief for Anxiety, Pain, Fatigue, and More. GreenStone Books; 2021.
48. Rafei P, Englund A, Lorenzetti V, Elkholy H, Potenza MN, Baldacchino AM. Transcultural Aspects of Cannabis Use: a Descriptive Overview of Cannabis Use across Cultures. Curr Addict Rep. 2023. doi: 10.1007/s40429-023-00500-8.
49. McHugh MJ, McGorry PD, Yung AR, Lin A, Wood SJ, Hartmann JA, et al. Cannabis-induced attenuated psychotic symptoms: implications for prognosis in young people at ultra-high risk for psychosis. Psychological Medicine. 2017;47(4):616-626. doi: 10.1017/S0033291716002671.
50. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. Schizophrenia Bulletin. 2016;42(5):1262-1269. doi: 10.1093/schbul/sbw003